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Abstract To investigate the extent and nature of the objective and subjective cognitive deficits and health-related quality of life (HRQOL) in adult outpatients with relatively well-controlled partial epilepsy without symptomatic aetiology, who were on carbamazepine (CBZ) monotherapy. Furthermore, we studied the influence of the epilepsy history and medication on various cognitive functions and the HRQOL.

56 outpatients (29 male, 27 female, mean age 41.3 years) with partial epilepsy were compared with 56 age-, gender-, and education-matched healthy controls. Patients were tested on attention, memory, speed of information processing, and executive functioning. Questionnaires aimed at measuring self-perceived cognitive functioning (CFQ) and HRQOL (SF-36) were administered. Mann Whitney-U tests were used to compare the two groups. Linear regression analysis was performed to identify the epilepsy and medication-related factors that are associated with cognitive functioning and HRQOL.

Patients scored lower on measures of attention ($P = 0.03$), learning ($P = 0.02$) and speed of information processing ($P = 0.00$). Mental aspects of HRQOL such as fatigue were lower ($P = 0.00$), whereas physical functioning was unaffected. These patients also expressed reductions in mental functioning as indicated by a low self-perceived cognitive functioning ($P = 0.01$). Age at onset, duration of epilepsy, seizure type, seizure frequency, localisation, years on CBZ, and CBZ dosage were not related to cognitive functioning or HRQOL.

Patients with partial epilepsy, even when able to maintain regular jobs, have impaired cognition and HRQOL that cannot be attributed to their epilepsy history or CBZ dosage or years of CBZ intake. Therefore, physicians should be more aware of their cognition and HRQOL, in addition to the antiepileptic drug regime.

Key words Partial epilepsy · Memory · Attention · Quality of life

Introduction

The incidence of localisation-related epilepsy in the Dutch population is 7.2/10.000. Eighty per cent of patients have relatively well-controlled epilepsy [1]. There are controversies about the definition of relatively well-controlled epilepsy and refractory epilepsy, particularly about how to estimate their severity and impact on the patient's life. In this study of outpatients from a specialised epilepsy centre we will refer to "relatively well-controlled" epilepsy if patients are treated with

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monotherapy, have one seizure per month or less and have regular jobs. Thanks to improved medical treatment the number of relatively well-controlled patients is increasing. Considering the fact that they maintain their regular jobs, seizures of these patients do not appear to interfere with their social functioning in the work situation [2]. These patients still report more cognitive complaints than healthy controls [3]. It has not been established, however, whether their cognitive functioning is impaired as well. It is thus not clear how widely epilepsy affects overall functioning in daily life in the subgroup of patients with relatively well-controlled localisation-related epilepsy.

In general, patients with localisation-related epilepsy report low self-perceived cognitive functioning [3], have cognitive deficits in different domains such as memory, attention, mental flexibility and motor speed [4], and perceive their health-related quality of life as lower than healthy controls on all aspects of mental functioning [5]. However, these studies incorporated patients with a wide range of aetiologies, medication types, and seizure frequencies, and maintaining a regular job was not an inclusion criterion. Therefore, the seizure severity and the impact on the patient's life varied in these studies. The only study into cognition that selected patients on the basis of their work situation referred to the patients as "normal epileptics" [2]. In that study, patients with primary generalised epilepsy and patients who were on polytherapy in 50% of the cases, were also included. Therefore, localisation-related epilepsy or relatively well-controlled epilepsy was not studied. Moreover, the control group in this study was not matched in age, gender, and educational level [2]. Therefore, it still remains unclear if cognitive functioning and HRQOL of the relatively well-controlled patients with localisation-related epilepsy are impaired.

The objective and self-perceived cognitive deficits and impaired HRQOL studied in patients with a wide range of epilepsy characteristics can be associated with different epilepsy-related factors such as age at onset, duration, seizure frequency, seizure type, localisation of the epileptogenic zone and medication-related factors [6]. Objective cognitive testing of patients with refractory epilepsy showed that factors such as age at onset [7] and duration [8] were associated with cognitive functioning. Earlier age at onset and longer duration of epilepsy are associated with diminished cognitive outcomes [7, 8]. On the other hand, in the study of "normal epileptics" age at onset, duration, seizure type, and seizure frequency could not explain the cognitive impairments [2]. Studies of mixed patient groups, ranging from relatively well-controlled to refractory epilepsy, revealed that an early age at onset, primary generalised epilepsies and symptomatic aetiology were associated with lower intellectual functioning [9, 10]. Furthermore, in patients with refractory epilepsy memory impairments are associated with localisation of the epileptogenic zone in the temporal lobe [11] and might also be negatively affected by drug treatment [12, 13]. Concerning self-perceived HRQOL, secondarily generalised seizures (GTCS) and higher seizure frequency have been negatively associated with HRQOL in mixed patient groups [14, 15]. In these studies, the seizure frequency of the patients ranged from no seizures during the last month to more than one per day, and fewer than half of these patients were employed full time. The patients' perceptions of the impact and stigma of their condition might be associated with impaired HRQOL as well [16].

The purpose of our study was to investigate whether patients with relatively well-controlled localisation-related epilepsy who are engaged in normal professional activities have objective and self-perceived cognitive deficits and impaired HRQOL compared with matched healthy controls. Patients who were administered with CBZ were selected, since this is the first drug of choice in the majority of patients with partial epilepsy. At the same time, cognitive side-effects are rarely reported in CBZ monotherpy treatment [17].

In addition, we studied whether epilepsy-related factors (age at onset, duration of epilepsy, seizure type, seizure frequency, and localisation) were associated with cognitive functioning and HRQOL in the patient group. Although no effect of medication was expected, two medication-related factors (years on CBZ and CBZ dosage) were also evaluated.

Patients and Methods

Patients

From January to March 1998 eligible outpatients with localisation-related epilepsy from three Stichting Epilepsie Instellingen Nederland outpatient clinics in the Netherlands (Heemstede, Amsterdam, and Utrecht) were identified in a stepwise fashion.

First, medical chart audits were performed to check inclusion criteria: (1) partial epilepsy; (2) carbamazepine (CBZ) monotherapy; (3) age from 18 years to 65. Exclusion criteria were: 1) present use of psychoactive drugs or antiepileptic drugs other than CBZ; 2) additional neurological or psychiatric disease according to DSM IV criteria; 3) severe perceptual deficits; 4) a history of head injury, status epilepticus, neurosurgery, or a neuropsychological evaluation within the last year. Furthermore, patients were selected if they have relatively well-controlled epilepsy, which was defined as one seizure per month or less, and the ability to have a regular job or attend a normal school [2]. This definition is derived from the definition of refractory epilepsy: patients who have had more than one seizure per month for at least two years that prevents them from normal social functioning [18]. The eligibility criteria based on information of the medical charts were met by 148 outpatients. All eligible patients were invited to participate by letter by their treating physician.

In the second step, all patients from whom informed consent was obtained were tested, additionally excluding those patients who had 8) no basic proficiency in the Dutch language, 9) a mental capacity comparable to an IQ ≤ 80, [19] or 10) mood disorders as indicated by a score of at least two standard deviations below the mean of healthy subjects on the Profile of Mood State questionnaire [20], since a high

prevalence of depression in patients with epilepsy affecting neuropsychological functioning has been reported [21]. Seventy patients signed the informed consent and were tested. Of these 70 patients, five patients had an IQ ≤ 80 and four had a mood disorder and thus had to be excluded. Another five patients were excluded from the 61 patients who remained, because their seizure frequency had changed in the meantime and turned out to be more than one per month. Since this study is part of a large intervention study, all patients, irrespective of cognitive complaints, were asked to visit the clinic ten times. Consequently, the major reason for non-participation of the 148 outpatients was the amount of time asked from each patient.

Methods

Standardised testing consisted of neuropsychological tests, a subjective evaluation of self-perceived HRQOL and self-perceived cognitive functioning, and a mood-state questionnaire (total duration 90 minutes). We successfully matched our patients with healthy controls on age, gender, and education. The control group was drawn from a large, cross-sectional study of the biological and psychological determinants of cognitive ageing, the Maastricht Ageing Study [22]. These healthy controls were recruited from the Registration Network Family Practices, a sample frame for research in primary care [23]. Participants had no medical conditions known to have an effect on cognition. All neuropsychological tests used in this study were administered to the healthy controls in the Maastricht Ageing Study, except for the TAP divided and alertness tasks. The questionnaire about self-perceived cognitive functioning (CFQ) was also part of the Maastricht Ageing Study. For the questionnaire about HRQOL, the SF-36 Health Survey, an individually-matched sample on age, gender, and education was drawn from other normative data. This questionnaire was validated among healthy Dutch-speaking residents of the Netherlands [24].

Objective Neuropsychological Status. Verbal memory was assessed with the Auditory Verbal Memory Test (VVLT). Selective attention was measured with the Stroop Color-Word Test (SCWT) [25]. Measures of divided attention were derived from the TAP Divided Attention task [26]. In this test, a visual and an acoustic task are presented simultaneously. The visual task consists of crosses that appear in a random configuration in a 4 × 4 matrix. The subject has to detect whether the crosses form the corner of the square. In the acoustic task the subject has to detect an irregularity in a regular sequence of high and low beeps. Speed of information processing was tested with the TAP Alertness with and without warning task [26]. A reaction time task with (cued RT) and without (simple RT) a warning signal can be compared. The test consists of four trials in an ABBA design each containing 20 presentations (A = with out cue, B = with cue). Executive control was measured with the Catagoric Word Fluency Task (Fluency) [27].

Self-perceived cognitive functioning was assessed using the Cognitive Failure Questionnaire (CFQ), [28] a 25-item self-report questionnaire that measures failures in daily life in four dimensions: absent-mindedness, problems with social interactions, difficulties remembering names and words, and difficulty with orientation. The total CFQ score ranged from 0 to 100, with higher scores indicating higher self-perceived cognitive functioning (CFQ).

Self-perceived health-related quality of life was assessed by means of the Short-Form Health Survey (SF-36) [29]. The SF-36 is a self-report questionnaire that covers the following eight dimensions of health: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. Two higher-order compound scores are computed: mental compound score (MCS) and physical compound score (PCS). Raw scores were converted linearly into a 0 to 100 scale, with higher scores representing better levels of functioning. Normative data for the healthy Dutch population were available [24]. In a large European study this questionnaire appeared to be a valid and reliable health status measure for descriptive studies in patients with epilepsy [30].

Statistical analysis

Student's t-tests for independent samples were used to determine if the neuropsychological performance of the patients, on the 13 different outcome measures summarised in Table 2, differed from the performance of healthy controls. The same test was carried out to compare the self-perceived cognitive functioning (CFQ) on the four dimensions and on the total score of this questionnaire, between the patients and the healthy controls. HRQOL of the patients was also compared with healthy controls on the eight-scaled scores of the SF-36 and the higher-order compound scores summarised in table 2 as well.

Linear multiple regression analyses were used to explore the association between cognitive status and the epilepsy history variables and medication-related variables: age at onset, duration, seizure frequency, seizure type, localisation of the epileptogenic zone, CBZ dosage, and years on CBZ. The individual effect of each variable on cognitive status was examined first. Then all variables that appeared to be influential were examined simultaneously in the multiple regression analysis. All of the nine dependent cognitive variables (see table 2), on which patients with epilepsy were compared with controls, were examined in the linear multiple regression analysis. The same procedure was carried out for the four dimensions of the self-perceived cognitive functioning questionnaire (CFQ) (absent-mindedness, problems with social interactions, difficulties remembering names and words, and difficulty with orientation) and for the HRQOL higher order compound scores (PCS and MCS).

Results

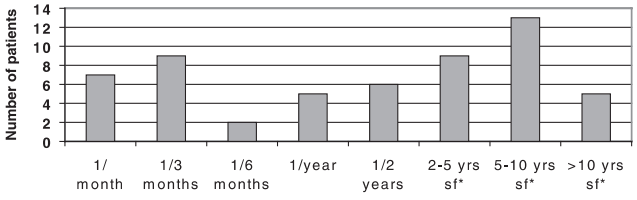
Table 1 and figure 1 show clinical characteristics of our sample. The gender distribution of the patients was 29 male and 27 female patients (n = 56). Patients' level of education [31] was classified as "low" in seven patients, as "average" in 27 patients and "high" in 22 patients. Twenty-three percent of the patients suffered from complex partial seizures. Combination of complex partial seizures with secondary generalisation accounted for another 52 %. Simple partial seizures combined with complex partial seizures or secondary generalisation accounted for the other 25 % of the 56 patients.

The clinical description of the seizures in combination with the EEG recordings enabled us to classify the epileptogenic zone: temporal lobe in 22 patients, frontotemporal lobe in 15 patients, frontal lobe in eight patients, other regions in eight, and undetermined in three patients. Lateralisation was left-sided in 27 patients, right-sided in 13 patients, and no definite lateralisation in 16 patients.

Table 1 Clinical characteristics of 56 outpatients with partial epilepsy on CBZ monotherapy

Variables	Mean ± SD	Range
Age (yrs)	41.3 ± 10.8	21.9–63.5
Age at onset of epilepsy (yrs)	24.5 ± 14.3	0–58
Duration of epilepsy (yrs)	17.9 ± 12.7	1–54
Duration CBZ therapy (yrs)	9.2 ± 6	2–26
Serum level CBZ (mg/l)	6.8 ± 2.2	3–13.1
Dosage (mg)	600 ± 300	100–1600

Fig. 1 Seizure frequency of 56 patients with relatively well-controlled partial epilepsy



* sf = seizure free

Table 2 shows the results of the neuropsychological testing. Patients with epilepsy had no difficulty with the immediate recall of newly presented information (VVLT Trial 1). The learning capacity of patients with epilepsy was not limited, in that they did benefit as much as healthy controls from repeated presentation of the same material. However, a smaller total amount of information was stored in the long-term memory of the patients (total recall). When patients had to recall the information 20 minutes after the initial presentation, they appeared to retrieve fewer words from long-term memory (delayed recall) ($P = 0.067$). These findings demonstrate that patients with epilepsy not only store less information in long-term memory, but also that they cannot easily retrieve this information at a later date. In addition, their selective attention, measured by the Stroop-Color-Word Test, showed reduced levels of information-processing capacity when reading colours (SCWT I). The patients were more susceptible to irrelevant visual information than the healthy controls (SCWT interference).

On divided attention tests we found that the patients had a significantly slower response time than the healthy controls. The speed of information processing of cued material was lower in the patients (TAP Alertness with warning). On the other hand, the patients had no difficulty with simple tasks like those requiring the generation of words from specific semantic categories (Fluency Test, $P = 0.244$). In addition, linear multiple regression analyses on cognitive outcome revealed that epilepsy history and medication-related factors were not associated with the results on cognitive subtests.

Self-perceived cognitive functioning (CFQ), measured with the total CFQ score, appears to be lower than the healthy controls ($P = 0.000$). The patients reported significantly more difficulties remembering names ($P = 0.001$) and, finding their way ($P = 0.000$) than did the healthy controls. Being absent-minded ($P = 0.041$) and, having difficulties with cognitive failures in social interactions ($P = 0.041$) was not significantly different from the healthy controls. In addition, no epilepsy or medication-related factor was associated with self-perceived cognitive functioning.

Self-perceived health-related quality of life (SF-36) appeared to be significantly lower on domains concerned with mental functioning ($P < 0.005$) for the patients than in the healthy controls. Vitality, measuring fatigue, was the most impaired mental subscale reported by the patients ($P = 0.000$). There was no significant difference between the two groups on the physical subscales (physical functioning and bodily pain).

There was no epilepsy or medication-related factor that could contribute significantly to health-related quality of life, measured with MCS or PCS.

Table 2 Neuropsychological test scores and scores on subscales of the SF-36, measuring health-related quality of life (HRQOL) of patients with epilepsy and healthy controls

Variables	Patients with Epilepsy ($n = 56$) Mean ± SD	Healthy Controls ($n = 56$) Mean ± SD	[a]$P <$
Neuropsychological test scores:			
Memory (VVLT):			
Trial 1 (nc)	5.7 ± 1.9	6.3 ± 1.7	NS
Total Recall (nc)	43.4 ± 9.8	49.1 ± 9.1	0.002
Delayed recall (nc)	9.1 ± 2.8	10.1 ± 3.0	NS
Attention (SCWT):			
Card I (s)	48.3 ± 12.1	39.9 ± 5.5	0.000
Interference (s)	66.7 ± 27.9	85.0 ± 34.6	0.003
TAP Divided Attention (ms)	728.0 ± 75.8	647.0 ± 69.4	0.000
Speed of information processing:			
TAP Alertness with warning (ms)	256 ± 49.7	213 ± 55.7	0.000
TAP Alertness without warning (ms)	264 ± 86.2	224 ± 80.0	NS
Executive function:			
Fluency (nc)	23.6 ± 6.6	25.0 ± 6.8	NS
HRQOL scores (SF-36):*			
Physical functioning	90.4 ± 11.8	90.8 ± 11.5	NS
Role physical	71.4 ± 33.8	87.2 ± 29.1	0.009
Bodily pain	76.0 ± 22.4	78.2 ± 21.2	NS
General Health	70.2 ± 18.5	80.2 ± 16.8	NS
Vitality	62.8 ± 15.9	75.4 ± 17.3	0.000
Social Functioning	81.4 ± 18.1	90.1 ± 16.4	0.009
Role emotional	76.7 ± 35.5	91.2 ± 25.6	NS
Mental Health	75.7 ± 15.8	80.8 ± 17.3	NS
Physical Compound Score (PCS)	50.1 ± 7.2	52.0 ± 7.9	NS
Mental Compound Score (MCS)	49.4 ± 9.0	54.3 ± 9.3	NS

See methods for explanation of abbreviations of variables. (s): seconds, (ms): milliseconds, (nc): number of correct responses. *Healthy controls for the SF-36 were derived from a different sample than the sample for the neuropsychological tests. Higher scores indicate better HRQOL.

[a] values of Student t-test comparisons between patients with epilepsy and healthy age, gender, and education matched controls.

Discussion

We studied adult outpatients with partial epilepsy, without symptomatic aetiology, on carbamazepine monotherapy. Since all these patients worked in a regular setting or attended regular schools, despite the fact that 50% still had seizures, we expected that their epilepsy severity would have a mild effect on their functioning in the work situation. Considering cognitive functioning, we found that these relatively well-controlled patients performed significantly worse on memory, selective and divided attention functions, and speed of information processing than the matched healthy controls. The diminished speed of information processing we found has also been established by pharmacological studies and might be due to medication [32]. REM sleep deprivation for example, caused by CBZ, might have affected cognitive performance, although the magnitude of this effect compared with other epilepsy-related characteristics remains controversial [33]. In accordance with other pharmacological studies on CBZ [34], we did not find an association between CBZ dosage or years of CBZ intake and impaired cognitive performance in our study.

Self-perceived cognitive functioning appears to be lower in adults with relatively well-controlled epilepsy than in healthy controls. A study by Corcoran and Thompson [35] revealed that patients with a late age at onset of epilepsy complained more about cognition. They suggested that patients might have more difficulties developing behavioural strategies that circumvent impaired functions at a later point in life. However, we did not find a relationship between age at onset and self-perceived cognitive functioning. Since seizure frequency, aetiology and medication-related factors were not reported in the study by Corcoran, a comparison with our subgroup was not possible.

Self-perceived health-related quality of life was poorer in patients with relatively well-controlled epilepsy than in matched healthy controls, especially on the subscales measuring mental functioning, whereas the physical subscales were unaffected. This finding is in line with the results of a large European study in which the SF-36 was used as well [30]. However, again in this study the epilepsy related factors varied greatly among the patients, and only 46% were working in a normal setting. The most impaired subscale in this study was "vitality" which is an index for fatigue. Further research is needed to investigate whether their self-perceived fatigue might have been caused by the extra effort needed to compensate for their impaired cognitive functioning, while working in normal settings. Replication of this study is needed with patients from a general hospital, since the patients in this study were selected from a specialised epilepsy center. Therefore, data can not be generalised to the general epilepsy population.

Another objective of this study was to explain the results in terms of factors that contribute to the cognitive impairments, impaired self-perceived cognitive functioning and impaired HRQOL. Unexpectedly, no significant relationship was established between the specific factors age at onset, seizure type, duration of epilepsy, seizure frequency, localisation, CBZ dosage, and years on CBZ on the one hand, and objective cognitive functioning, self-perceived cognitive functioning or HRQOL on the other hand [2]. This finding that the investigated factors cannot clarify the cognitive impairments is supported by studies in newly-diagnosed patients with partial epilepsy. These patients show cognitive impairments as well, despite the fact that factors such as anti-epileptic medication, age at onset of epilepsy, duration of epilepsy, and frequency of seizures are excluded. In this study, the causes for their epilepsy, either through biochemical processes or through the underlying neuronal damage, appear to be the most important factor leading to cognitive impairments. Concerning self-perceived health-related quality of life the patients' negative observation of themselves and of their epilepsy together with a different attitude from the social context affects overall well-being and can better explain the observed differences with healthy controls [36]. Ryan demonstrated that perceptions of stigma in epilepsy patients were more strongly influenced by self-perceptions than by the objective facts of epilepsy [16].

It remains unclear whether the underlying cause for their epilepsy, the different attitudes towards these patients in a social context, or a combination of both can explain the impaired cognitive functioning and impaired HRQOL.

Moreover, a nonspecific effect of having a chronic illness can not be excluded and therefore, a comparison with a patient group without a CNS disease might have been a valid additional control group. Loiseau [2] incorporated a control group of patients without a CNS disease and, although there are differences from our study design, memory impairments could not be attributed to a nonspecific effect of having a chronic disease.

In conclusion, our results show that relatively well-controlled patients with partial epilepsy do have cognitive deficits and perceive their cognitive functioning as low compared with healthy controls. We determined that their HRQOL of mental functioning is significantly lower than healthy controls' HRQOL. However, most epilepsy-related factors known to alter cognitive performances or HRQOL in patients with refractory epilepsy could not be identified in this subgroup of patients.

In this subgroup of patients alterations in the seizure history, and consequently changes in CBZ dosage, do not seem to contribute to impaired cognition or HRQOL. Nonetheless, physicians should also be aware of the objective cognitive deficits, and the lower self-perceived

HRQOL and cognitive functioning, in these relatively well-controlled patients with localisation-related epilepsy. Subsequently, physicians can encourage patients to participate in cognitive rehabilitation programs.

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